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Depressive Symptoms and Metabolic Markers of Risk for Type 2 Diabetes in Obese Adolescents

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Abstract

Objective—Although higher rates of depression are found among individuals with type 2 diabetes, it remains unknown if the presence of depressive symptoms is associated with heightened metabolic risk for the development of type 2 diabetes among youth. The objective of this study was to evaluate whether depressive symptoms in obese adolescents are associated with impaired β-cell function relative to insulin sensitivity (oral disposition index [oDI]) and/or dysglycemia or prediabetes, predictors of type 2 diabetes development.

Research Design and Methods—Fasting and oral glucose tolerance test (OGTT)-derived indices of glucose tolerance, insulin sensitivity, secretion and oDI were evaluated in obese youth (n=56, age 15.0 ± 1.6 y, 68% female). The Children's Depression Inventory (CDI) was utilized to determine depressive symptomatology.

Results—Despite no association between depressive symptoms and measures of adiposity, youth with higher depressive symptoms had 1) significantly higher fasting and stimulated glucose levels (13% higher glucose area under the OGTT curve), 2) ~50% lower oDI, and 3) a 50% frequency of prediabetes.

Conclusions—These data point to an important relationship between depressive symptoms and a heightened metabolic risk for type 2 diabetes in obese adolescents, including prediabetes and impairment in β-cell function relative to insulin sensitivity. While the directionality of these relationships is unknown, it should be determined if treating one disorder improves the other or vice versa.

Key Terms

obesity; depression; type 2 diabetes; insulin secretion; insulin sensitivity; prediabetes; impaired glucose tolerance

Introduction

Adolescents often suffer from depressive symptoms, which can be associated with a variety of adverse effects on physical and metabolic health. The co-occurrence of depression and chronic medical illness, including diabetes, has been shown in multiple studies in adults and children; however, the directionality of this relationship is unclear (1–6). Moreover, although previous studies have linked depressive symptoms with markers of decreased insulin sensitivity (increased fasting insulin and Homeostasis Model Assessment (HOMA)

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levels) in non-diabetic youth (7–9), no pediatric studies have examined potential associations between depressive symptoms and metabolic risk markers for type 2 diabetes. In longitudinal studies of adults without diabetes, oral disposition index (oDI), a measure of insulin secretion relative to insulin sensitivity, is shown to be the strongest metabolic predictor of future diabetes (10, 11). In youth, oDI correlates strongly with clamp-derived DI, declines across the spectrum of glucose intolerance, and predicts the development of dysglycemia after 2 years (12, 13). Therefore, the primary objective of this study was to evaluate the relationships between self-endorsed depressive symptoms and metabolic risk markers for type 2 diabetes including dysglycemia and β-cell function relative to insulin sensitivity, oDI, measured during oral glucose tolerance testing (OGTT) in obese non-diabetic adolescents.

Methods

A total of 56 obese adolescents (age 15.0 ± 1.6 y, 68% female, 61% non-Hispanic white, 32% non-Hispanic black, 7% bi-racial), including 23 girls with untreated polycystic ovary syndrome (PCOS), who were participants in our National Institutes of Health-funded studies enrolling obese adolescents (R03HD057532, K23KD061598) who had completed baseline OGTT and standardized questionnaires for depression screening. The questionnaires were administered prior to giving the results of the OGTT testing to the participants. Participants were patients referred to an obesity clinic as part of their medical care who were invited to participate in these IRB-approved protocols. When a patient expressed interest, a research assistant described the study procedures, assessed eligibility, and answered questions, and obtained informed assent/consent prior to participation. Data from some of these participants were reported previously (14–17). Eligibility criteria were: BMI ≥ 95^{th} percentile, age 12–18 years, and Tanner stage III–V puberty. Exclusion criteria included chronic disease or medications associated with glucose intolerance, diabetes, and syndromic obesity, such as Prader-Willi syndrome or hypothalamic obesity.

Study Procedures

Study procedures were performed during a single visit to the Pediatric Clinical and Translational Research Center. Glycosylated hemoglobin (HbA_{1C}) and a standard 2-hour OGTT (1.75 g/kg, maximum 75 g) were performed to evaluate glucose tolerance and calculate insulin sensitivity and secretion indices and oDI. Blood samples were drawn at −15, 0, 15,30, 60, 90, and 120 minutes for determination of glucose and insulin levels as previously described (14, 18). Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentrations were determined by multiplexed immunoassay using fluorescent microspheres(Millipore)and the Luminex-200 system (Luminex Corporation).

The Children's Depression Inventory (CDI) was used to assess depressive symptoms and results were reviewed immediately by a research team member who had access to consultation with a licensed clinical psychologist if necessary (19). The CDI is a widely used measure of depressive symptoms comprised of 27 items loading on five primary factors: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. The measure was originally normed on a sample of 1,266 public school students ranging in age from 7–16 (47% male; 77% Caucasian and 23% African American, Native American or Hispanic; largely middle class with wide socioeconomic range), and was also assessed on a clinical sample of 134 adolescents with depressive disorders (47% male; 62% Caucasian and 34.3% African American; 67.9% from lower socioeconomic status) (19). The CDI is repeatedly shown to be a reliable and valid measure of depressive symptoms with high test-retest reliability and the capacity to detect changes in depressive symptoms over treatment (20, 21).

Calculations

Fasting glucose and insulin were obtained from the baseline measurements of the OGTT. The inverse of fasting insulin (1/fasting insulin) was utilized as a surrogate estimate of insulin sensitivity (22). Early phase insulin secretion during the OGTT was expressed as the insulinogenic index (IGI) or the ratio of the incremental response of insulin to glucose at 30 minutes of the OGTT (IGI_{30}) (13). One subject had a 30 minute insulin level that was essentially the same as the fasting insulin, producing a zero value (−0.09), which was included in the statistical analysis. The oDI was calculated as IGI_{30} × 1/fasting insulin (13). One subject with a low CDI score had a missing value for glucose at 30 minutes during the OGTT and thus had missing data for IGI_{30} and oDI.

Statistical Analysis

Analyses were conducted using SPSS 19.0 and all tests were two-tailed. Goodness-of-fit tests (Kolmogorov-Smirnov and Anderson Darling) and quantile-quantile (Q-Q) plots were used to assess normality of distribution.

Individuals with lower versus higher total CDI scores (<13 *vs*≥13) were compared. The utility of a categorical approach at this cut-point is accepted as useful for the purposes of screening for the potential of a depressive disorder (23–25). This cut-point has also been used in a previous pediatric study evaluating associations between depressive symptoms and fasting insulin outcomes (8). The chi-square test for independence or the Fisher's exact probability test was used to compare categorical variables. Two-sided t tests were used to compare normally distributed continuous variables and Mann Whitney U tests to compare non-normally distributed continuous variables. Statistical power was determined to be >90% to detect a 50% difference in oDI, the primary outcome, among the CDI groups, $\alpha = 0.05$.

CDI scores as a continuous variable were not normally distributed, even after applying standard transformation approaches, thus nonparametric Spearman rank-order correlation coefficients were calculated to quantify the associations between CDI scores, anthropometric measures, indices of glucose tolerance and oDI. This strategy was used in addition to dichotomizing the CDI data because existing literature suggests that even sub-threshold depressive symptomatology is associated with inferior insulin sensitivity in youth (7, 9). CDI T-scores, rather than total scores, were utilized in correlation analyses because the T-score already accounts for age and gender. Partial correlation coefficients controlling for BMI were also calculated to evaluate associations between depressive symptoms and glucose homeostasis parameters. Natural logarithm transformation was performed to accommodate skewness of the observed data when plotting the relationship between the CDI and the oDI. Statistical power was determined to be 80% to detect a linear association ($r = 0.40$, $\alpha = 0.05$) between the CDI total score and the oDI. In addition, we evaluated whether the CDI total scores were associated with a worse metabolic state (lower oDI, higher fasting, 2-hr, and AUC glucose values) while also accounting for gender, race, age, and BMI, by performing standard multiple regressions using metabolic outcomes of interest as the dependent variables and CDI score, gender, age, race, and BMI as the independent variables.

Results

The mean CDI score for the study population was 9 ± 8; the median score was 7; range 0–30. Median CDI scores did not vary by race (7.0 in non-Hispanic whites, 7.5 in non-Hispanic blacks, and 6.5 in biracial participants, $p = 0.84$) and the distribution of CDI scores was the same for males and females ($p = 0.53$). Demographic, anthropometric, and metabolic characteristics of the participants grouped by CDI score cut off of 13 are shown in Table I. There were no significant differences in age ($p = 0.66$), sex ($p = 0.75$), BMI ($p =$

0.95), or waist circumference ($p = 0.83$) (Table 1), nor were there significant linear relationships between CDI score and these measures. There was a trend for those with higher depressive symptoms to be of non-Hispanic white race ($p = 0.06$).

HbA_{1C} and fasting insulin did not differ significantly among the groups (Table I, $p = 0.24$ for HbA_{1C} and $p = 0.16$ for fasting insulin). However, fasting and 2-hr glucose levels were significantly higher in the group with higher CDI scores (Table I). Fifty percent of the participants with CDI scores ≥13 had evidence of pre-diabetes (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) as compared with 19% of the participants with lower CDI scores (Table I, $p = 0.04$). The percentage of participants with PCOS did not differ among the groups (Table I, $p = 1.0$).

The acute insulin response to glucose, IGI_{30}, during the OGTT was ~41% lower ($p = 0.02$), and the oDI was ~50% lower ($p = 0.001$) among those with greater depressive symptoms (Table I). The group with higher CDI scores also had significantly higher glucose AUC, but the insulin AUC was not different during the OGTT ($p = 0.91$), demonstrating relative insulin deficiency in this group (Table I).

Associations between log-transformed CDI T-score and (A) fasting glucose, (B) OGTT 2-hr glucose, (C) OGTT glucose AUC and (D) oral disposition index (oDI) are shown in Figure I (subjects with CDI total score < 13 are represented by empty circles and CDI total score ≥ 13 are represented by filled circles). There were significant associations between the CDI and OGTT 2-hr glucose ($r = 0.329$, $p = 0.013$; adjusted for BMI $r = 0.364$, $p = 0.007$) and oDI ($r = -0.337$, p = 0.013; adjusted for BMI $r = -0.435$, $p = 0.003$). Generally there were no correlations between insulin sensitivity indices and CDI scores.

To clarify whether the associations with CDI were independent of the demographic and anthropometric characteristics of the cohort, standard multiple regression analyses were conducted with the metabolic variables (fasting glucose, OGTT 2-hr glucose, OGTT glucose AUC and oDI) as the dependent variables and CDI, gender, age, race, and BMI as the independent variables (Table II). CDI was a significant contributor to OGTT glucose AUC and oDI. The model explained 21% of the variance in OGTT glucose AUC ($R^2 = 0.209$, $p = 0.041$), and only CDI contributed significantly ($\beta = 0.348$, $p = 0.011$). The model explained 23% of the variance in oDI ($R^2 = 0.233$, $p = 0.02$). Significant contributors to the oDI score were the CDI score ($\beta = -0.262$, $p = 0.047$) and race ($\beta = 0.273$, $p = 0.037$; non-white race was associated with higher oDI). Gender, age, and BMI did not contribute significantly to the models.

There were 23 girls with untreated polycystic ovary syndrome who were included in the analysis. As women with PCOS are known to have greater risk for impaired glucose tolerance and type 2 diabetes, this may have impacted the measured relationships. When this group was analyzed separately, the relationship between CDI and oDI was found to be very significant among this group of girls ($r = -0.521$, $p = 0.015$). Associations between CDI score and the other parameters of pre-diabetes (fasting, OGTT 2-hr and AUC glucose) were not significant in this smaller sample.

Discussion

In this study we found that higher levels of depressive symptoms in obese youth were associated with 1) lower insulin secretion relative to insulin sensitivity (oDI), indicative of impaired β-cell function, 2) higher fasting and OGTT-stimulated glucose levels indicative of lower glucose tolerance, and 3) higher frequency of prediabetes (either IFG or IGT). This is despite no association between CDI score and BMI or waist circumference. In cross-sectional and longitudinal cohort studies of youth without diabetes, insulin secretion

adjusted for insulin sensitivity is a strong metabolic predictor of IGT and diabetes (12, 13, 26, 27). In multiple linear regression models, CDI scores contributed significantly to OGTT glucose AUC and oDI values when accounting for effects of race, gender, age, and BMI. We also found non-white race to be associated with higher oDI. This finding is in agreement with our previously published data showing that the quantitative relationship between insulin sensitivity and first-phase insulin differs by race, with non-diabetic black children having greater first-phase insulin secretion, as compared with their white peers with similar BMIs (28).

Our findings that youth who endorse more depressive symptoms have a higher frequency of pre-diabetes would suggest a heightened risk for the future development of type 2 diabetes in them. Findings from the Treatment Options for Type 2 Diabetes in Youth (TODAY) study revealed rates of depression in adolescents with diabetes were comparable to the rates of depression in obese non-diabetic adolescents (29). The TODAY study cohort was comprised of patients recruited after the diagnosis and start of treatment of diabetes, and more than 80% of the participants were of minority race/ethnicity. In contrast, our study population was restricted to very obese patients; primarily white adolescent females who were seeking obesity treatment. Thus, the results may not be comparable to this previous study. Furthermore, the results of our study are not generalizable to less obese individuals or to adolescents with diagnosed depression. Nevertheless, very obese adolescents have the highest risk of developing diabetes during childhood and addressing potentially modifiable risk factors is therefore relevant.

The prevalence of depressed mood is reported to be higher among males with type 2 diabetes than those with type 1 diabetes in the SEARCH for Diabetes in Youth study (30). Currently, the directionality of the association between depressed mood and type 2 diabetes in this pediatric cohort of patients is unknown. A prospective pediatric study evaluated depressive symptoms, along with fasting measures of insulin sensitivity, in children aged 5–13 years at a baseline visit, and again at a mean follow-up of 6 years (8). Depressive symptoms at baseline were a significant predictor of fasting insulin and HOMA levels at follow-up after controlling for BMI and other confounders; however, insulin secretion measures were not obtained to determine β-cell function relative to insulin sensitivity. A few additional pediatric studies have also found associations of indices of depression with fasting measures of insulin sensitivity (9, 31). Our study design which included only very obese insulin resistant adolescents (BMI ≥ 95^{th} percentile; mean BMI 38.0 ± 7.7 kg/m^2) who were presenting to a tertiary care obesity center for treatment, may have precluded us from finding a relationship between depressive symptoms and insulin sensitivity. We postulate that the degree of obesity may have overshadowed any effect of depression on measures of insulin sensitivity performed in this study. We did not adjust for the effect of puberty on insulin sensitivity because all of the participants were at least Tanner stage III, and our previous research demonstrates that pubertal insulin resistance accounts for a fraction of that which is imparted by severe obesity (32, 33).

Many of the girls in our study had signs of untreated PCOS, which is known to be associated with greater prevalence of pre-diabetes and depression (17). Although the percentage of females with PCOS in each CDI group (CDI < 13 or ≥ 13) was the same, there was a significant association between the CDI and oDI in these girls which is of clinical interest and should be evaluated further in future studies. An additional limitation of our study is the lack of information on socioeconomic status and family environment, which will be important to include in future investigations. Our results did indicate a potential race effect on the relationship between the CDI score and the oDI which has not been reported in pediatrics and indicates need for further study in a larger more diverse study sample.

Previously proposed mechanistic pathways linking anxiety, emotional stress, and depressive symptoms to adverse cardiometabolic risk factors include greater potential for poor quality sleep (34), sedentary lifestyle (35, 36), activation or dysregulation of the hypothalamic-pituitary-adrenal axis leading to chronically increased levels of catecholamines (37), and systemic inflammation and oxidative stress (38). Advances in the understanding of the pathophysiology of type 2 diabetes and depression support a role for chronic inflammation and oxidative stress in each of these conditions and provide evidence that shared inflammatory mechanisms may link these conditions biologically (39, 40). While our study was not designed to evaluate the mechanisms of this relationship, it indicates the need for further studies examining such factors.

In conclusion, in this cohort of obese adolescents, higher depressive symptoms was associated with evidence of impaired β-cell function relative to insulin sensitivity and more dysglycemia compared with their equally obese peers who did not validate depressive symptoms. From a clinical perspective, the relationship between depressive symptoms and glucose tolerance abnormalities in obese adolescents at risk for type 2 diabetes should be considered while evaluating these youth. From a research perspective, these relationships should be investigated further to determine the directionality of the association, i.e. if early recognition and treatment of depressive symptoms improves metabolic risk for type 2 diabetes.

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Abbreviations

AUC	area under the curve
BMI	body mass index
CDI	Children's Depression Inventory
HbA_{1C}	glycosylated hemoglobin
HOMA	Homeostasis Model Assessment
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IRB	Institutional Review Board
IGI	insulinogenic index
oDI	oral disposition index
OGTT	oral glucose tolerance test
PCOS	polycystic ovary syndrome

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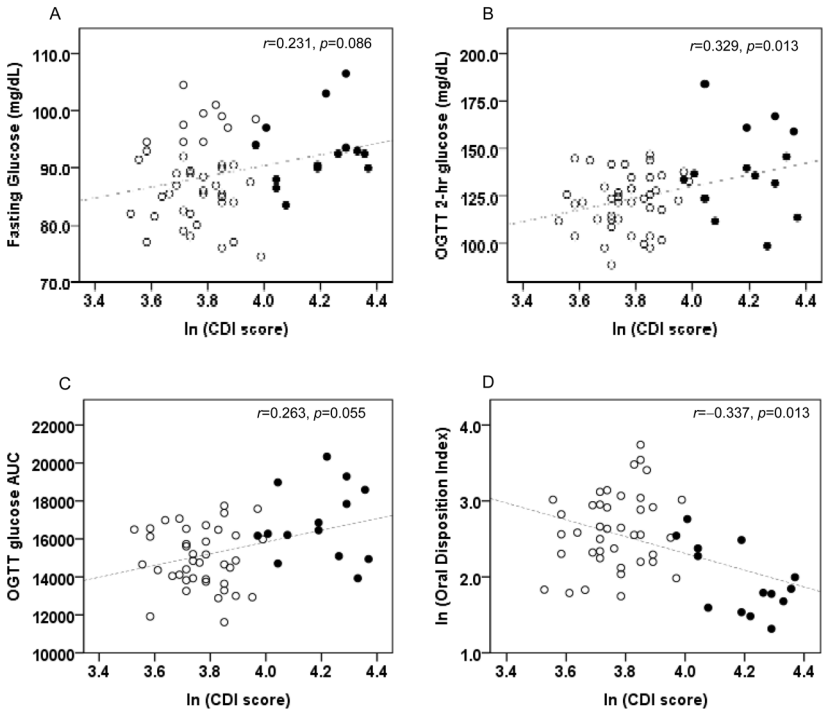

Figure I.

The correlation between log-transformed CDI score and (A) fasting glucose, (B) OGTT 2-hr glucose, (C) OGTT glucose AUC and (D) oral disposition index (oDI). Subjects with CDI total score < 13 are represented by empty circles and CDI total score ≥ 13 are represented by filled circles.

Table I

Demographic, Anthropometric, and Metabolic Characteristics of Participants According to Depressive Symptoms (CDI score ≥ 13 indicates higher depressive symptoms)

Variable	CDI score < 13 (6 ± 3; range 0 – 12) n = 42	CDI total score ≥ 13 (22 ± 5; range 13 – 28) n = 14	*P*
Age	14.9 ± 1.7 (range 12.1 – 18.1)	15.1 ± 1.4 (range 12.7 – 17.4)	0.66
Sex (n; %)			0.75
Female	27 (64.3)	10 (71.4)	
Male	15 (35.7)	4 (28.6)	
Race (n; %)			0.06
Non-Hispanic Black or bi-racial	20 (47.6)	2 (14.3)	
Non-Hispanic White	22 (52.4)	12 (85.7)	
BMI (kg/m^2)	38.0 ± 7.2 (range 28.2 – 55.5)	38.1 ± 9.1 (range 27.8 – 61.6)	0.95
BMI Z-score	3.3 ± 1.5 (range 1.53 – 8.31)	3.2 ± 1.6 (range 1.55 – 7.68)	0.87
Waist circumference (cm)	109.4 ± 17.8	110.6 ± 19.2	0.83
HbA_{1C} (%)	5.4 ± 0.4	5.5 ± 0.4	0.24
Fasting insulin (μU/mL)	32.2 ± 19.4	36.7 ± 16.1	0.16
Fasting glucose (mg/dL)	88 ± 7	93 ± 6	**0.028**
OGTT 2-hr glucose (mg/dL)	122 ± 15	139 ± 23	**0.020**
Impaired fasting glucose	4.8%	14.3%	0.26
Impaired glucose tolerance	14.6%	42.9%	0.055
IFG or IGT	19.0%	50.0%	**0.037**
Diagnosed PCOS (females)	59.3%	60.0%	1.0
IGI_{30}	4.49 ± 2.92	2.73 ± 1.57	**0.024**
oDI	15.2 ± 8.6	7.8 ± 3.7	**0.001**
OGTT Insulin AUC	22,090 ± 14,680	22,597 ± 10,429	0.91
OGTT Glucose AUC	14,963 ± 1,564	16,835 ± 1,919	**0.001**

Table II

Results of Multiple Regression Analysis of Relationships between Measures of Diabetes Risk and CDI score

Dependent Variable	Independent Variables	Standardized β	β *p value*	Model R^2	ANOVA *P value*
OGTT glucose AUC	CDI	**0.348**	**0.011**	**0.209**	**0.041**
	Gender	−0.088	0.502		
	Age	−0.022	0.864		
	Race	−0.238	0.075		
	BMI	0.077	0.552		
oDI	CDI	**−0.262**	**0.047**	**0.233**	**0.020**
	Gender	−0.181	0.157		
	Age	0.157	0.223		
	Race *	**0.273**	**0.037**		
	BMI	0.207	0.837		
Fasting glucose	CDI	0.263	0.059	0.125	0.231
	Gender	−0.177	0.191		
	Age	0.094	0.486		
	Race	−0.119	0.381		
	BMI	−0.012	0.927		
OGTT 2-hr glucose	CDI	**0.300**	**0.030**	0.149	0.139
	Gender	0.017	0.898		
	Age	0.070	0.597		
	Race	−0.174	0.196		
	BMI	0.036	0.782		

* Race is white=0 versus non-white race=1 in the model.